“Treatment interruption in children can be used as an alternative to continuous therapy”

Karina Butler
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Outcomes in perinatally infected children (UK and Ireland)

- Increasing proportion of infected children on ART
- Mortality rates declined by 80%, progression to AIDS by 50% between 1997 and 2001/2 (and sustained since)
- Hospital admission rates declined by 80%, but number of hospital admissions by 25% only (due to increasing number of infected children)
- Improvements more marked for children than infants
- Improvements in survival for infants, but not in rates of disease progression

Gibb et al, BMJ 2003; 327;1019
Doerholt et al, PIDJ. 2006; 25(5):420-6
Judd et al, CID. 2007;45(7):918-24
Not all treatment interruptions are the same!

- An **planned** break in continuous daily therapy
- Strategic use of ARVs
- For Selected individuals/groups
- In certain situations

**Interruption**
- In Primary infection
- Chronic infection
  - CD4 guided
    - With viral rebound
  - Very Short Interruptions
    - No viral rebound
- Chronically infected children, nonadherent & failing therapy
  - Holding measure
The ARV Pendulum

**PRE-HAART** *(PRE 1996)*
*Save the ammo - it's not so great anyway*

**1995 - 2000)** HAART
*Great stuff-hit early hit hard*

**GETTING TO KNOW HAART** *(2001-2006)*
*Hold on - may be too much toxicity*

**NEW AND IMPROVED HAART**
*Early treatment = better outcomes*

**TODAY**
*>350 - 500 better than <350*
  - SMART (subgroup
  - NA-ACCORD cohort
  - ART Cohort collaboration  
Earlier initiation of Therapy: Infants

- **CHER**
  - Immediate vs deferred
  - Reduced mortality
  - Improved neurodevelopmental outcomes
    - NEJM 2008; 359:233-44
    - AIDS 2012, DOI:10.1097/QAD.0b013e328355d0ce
Emerging dogma

- Early treatment of infants must be followed by life long therapy
- Children—can never interrupt their daily regimen

Today's certainty - tomorrow's folly
Real Life Balance

- Are all data based on studies in adults necessarily applicable to children?
- Are TI are a realistic alternative to continuous treatment?
  - When
  - For whom
- Can safe TI be construed?
- Globally - are TI in fact a necessity?
HAART

☑ Simple formulations
☑ Easy to take
☑ No Drug Toxicity

☑ Cheap
☑ Readily Accessible
☑ Plenty for all

Continuous Therapy

Treatment Interruption
HAART

Continuous Therapy

- Simple formulations
- Easy to take
- No Drug Toxicity
- Perfect Adherence
- Cheap
- Readily Accessible
- Plenty for all

Treatment Interruption

- ARV PK/PD
- Infant immunology
- Family dynamic
- Adolescence
- Logistics
Planned Treatment Interruption

Hopes

- Safe
- Reduce ARV exposure
- Reduce toxicities
- Improve adherence and retention in care
- Enhance quality of Life
- Reduce cost
- Increase ARV rollout

Fears

- AIDS events and encephalopathy in infants
- Rapid decline in CD4 and irreversible immunologic changes
- Refusal/reluctance to resume therapy
- Loss of first line therapy
- Accumulation of resistance mutations
We need treatment strategies that........

- manage HIV, cradle to grave (inc. adolescence)
- recognise that children not just simply little adults
- exploit availability and potency of ARVs
- are designed to afford maximum benefit to all infected children
A case to ponder: in utero transmission

- Infant PCR
  - D1 91cpm
  - D10 <50
  - D15 detectable < 400 VL
  - D33 >50,000cpm

- CD4 always >30%
Mom cried stop!

- Infant PCR
  - D1 91 cpm
  - D10 <50
  - D15 detectable < 4000000
  - D33 >50,000 cpm

- CD4 always >30%
The effect of short-course ART in PHI
Final results from an international randomised controlled trial
SPARTAC
Sarah Fidler
for SPARTAC Trial Investigators

PHI randomised to SOC, ART-12 or ART-48 wks, interrupted & ave. follow up of 4 yrs

No difference between groups for AIDS, death or SAEs

- In contrast to SMART, no rebound in IL6 post interruption and a drop in d-dimers
- CD4 increases after initiation of longterm therapy similar across groups
- No difference in resistance markers
- No difference in virologic failure after initiation of long term therapy

IAS Rome 2011
Conclusion

Interruption of ART in PHI had no evidence of harm; development of drug resistance, or impaired CD4 recovery after starting long-term ART.

IAS Rome 2011
Optimising Paediatric HIV Therapy,

- 43 infants, >24 mos ART randomised to PTI or CT
- Restart if CD4 <25% or 1/3 drop
- 80% restart by 9.9 mos
- 20% had not met restart criteria
- No difference in clinical events
- No difference in CD4/VL 18 mos post randomisation
"did not exclude the possibility of treatment interruption for infants with higher CD4" Wamalwa and Jones

Wamalwa et al, CROI 2012. #27
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ART-Def 125</th>
<th>ART-40W 126</th>
<th>ART-96W 126</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (weeks) (IQR)</strong></td>
<td>7.1 (6.4 – 8.9)</td>
<td>7.4 (6.6 – 8.7)</td>
<td>7.5 (6.6 – 9.0)</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>59</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td><strong>Median weight-for-age</strong></td>
<td>-0.6 (-1.3 to 0.2)</td>
<td>-0.8 (-1.4 to 0.2)</td>
<td>-0.7 (-1.6 to 0)</td>
</tr>
<tr>
<td>Z-score (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median CD4% (IQR)</strong></td>
<td>36 (29 – 44)</td>
<td>35 (30 – 42)</td>
<td>34 (29 – 40)</td>
</tr>
<tr>
<td><strong>CD4/mm³ (IQR)</strong></td>
<td>2021 (1584 – 2926)</td>
<td>1978 (1476 – 2789)</td>
<td>2058 (1520 – 2743)</td>
</tr>
<tr>
<td><strong>CDC stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N + A</strong></td>
<td>118 (95%)</td>
<td>121 (96%)</td>
<td>117 (93%)</td>
</tr>
<tr>
<td><strong>% Mothers not</strong></td>
<td>12.0%</td>
<td>10.3%</td>
<td>9.5%</td>
</tr>
<tr>
<td>receiving pMTCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breastfeeding N (%)</strong></td>
<td>12 (9.6%)</td>
<td>13 (10.3%)</td>
<td>13 (10.3%)</td>
</tr>
</tbody>
</table>
Clinical status at end of trial

August 2011

<table>
<thead>
<tr>
<th></th>
<th>ART-40W N: 143</th>
<th>ART-96W N: 143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children never started continuous ART (%)</td>
<td>30 (25%)</td>
<td>46 (33%)</td>
</tr>
<tr>
<td>Median CD4% (IQR)</td>
<td>32 (28-36)</td>
<td>30 (24-34)</td>
</tr>
<tr>
<td>Median CD4 Count (cells/mm³) (IQR)</td>
<td>1053 (773-1399)</td>
<td>967 (741-1269)</td>
</tr>
<tr>
<td>Anthropometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Weight for age Z-score (sd)</td>
<td>-0.62 (0.89)</td>
<td>-0.56 (0.79)</td>
</tr>
<tr>
<td>• Height for age Z-score (sd)</td>
<td>-1.4 (0.91)</td>
<td>-1.4 (1.06)</td>
</tr>
<tr>
<td>Number hospitalizations</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Grade 3 or 4 events (#children)</td>
<td>181 (75)</td>
<td>157 (71)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>(Def. 9/38)</td>
<td>5/22</td>
</tr>
<tr>
<td></td>
<td>2/17</td>
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</table>
Proportion of children on ART

Overall proportion of time spent on ART
- ART-Def: 81%
- ART-40W: 70%
- ART-96W: 69%
Treatment interruption after primary infection in infancy

• Safe. No evident disadvantage in;-
  – Clinical events
  – Development of encephalopathy
  – Re-suppression post reinstitution of treatment
  – Switch to second line therapy

• May identify the chronic long term-non progressors

• Selection of infants critical (asymptomatic, high Cd4)

• Optimal duration of initial treatment to be determined

• Effective drug/cost sparing strategy

• Family respites

• Important to continue study and to further examine for any subtle areas if disadvantage
Course 0 - 9 yrs
Not time yet......
Long Term consequences of planned treatment interruptions in HIV infected children: results from the TICCH (Treatment Interruption in Children with Chronic HIV-Infection/PENTA 11

- CD4 guided PTI to max of 48 weeks
- Median f/u 4.5 yrs
- Primary endpoints:
  - CDC C/death/CD4 < 15% or 200 x 10^6/l
  - CT vs PTI: 4 vs 48% time off ART
  - No serious clinical events
  - Lower nadir predicted faster CD4 decline
  - Younger children & higher nadir predicted being off tx for 48 wks and better recovery
  - 86%-CT, 82% PTI had VL< 50c/ml 2 yrs from trial end

AIDS 2010,24 ;231-241
3rd HIV Paediatric workshop Rome 2011
New drugs never used before prescribed after baseline, by class

<table>
<thead>
<tr>
<th>Class</th>
<th>P-value</th>
<th># of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>0.06</td>
<td>≥2: 100%, 1: 60%, 0: 40%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.55</td>
<td>≥2: 100%, 1: 60%, 0: 40%</td>
</tr>
<tr>
<td>PI</td>
<td>0.92</td>
<td>≥2: 100%, 1: 60%, 0: 40%</td>
</tr>
</tbody>
</table>

P=0.06 comparing arms

% of children

CT PTI

P=0.55

CT PTI

P=0.92

CT PTI
PENTA 11: trends in C4 counts during and following PTI

Slide courtesy Prof Nigel Klein and Immunology subgroup
CD4 RA % of absolute CD4

Including all children in trial
Observed and median values at selected time points shown, by arm

Slide courtesy Prof Nigel Klein and Immunology subgroup
Treatment interruption in chronic infection; PENTA 11

- Did not disadvantage children
- No difference in exposure to new drug classes between arms
- Did not impede CD4 recovery on re-initiation
- Did not prevent virologic suppression on re-initiation
- No difference in neurocognitive outcome between arms (Poster CROI Seattle 2012)
Adolescents & Antiretroviral Therapy

- No point
- No future
- Poor Adherence
- Want a “normal life”

“I noticed with me tablets towards the end, I got very lackadaisical with them.

“I just felt like..... why do I have to take it...cause you feel fine and you think there’s no point to this”

Sometimes my body .......... just won’t swallow them”
V. Short Cycle Therapy - No Rebound

- **Viral dynamics**
  - Adults: VL >50c/ml 1-2 weeks post stop.
  - Children: >70% VL < 50c/ml D14 post stop EFV Based: > 80%

- **Drug levels**
  - Plasma EFV concentrations predicted to exceed 95% inhibitory concentration for Wt-virus for median of 4.4 - 21.2 days (adults)
    - Ribaudo *CID* 2006;42;401-407

- **Interplay of adherence, drug levels and duration of interruption**
# SCT trials in adults

## THE FOTO STUDY

48 week Results to assess durability of the strategy of taking Efavirenz, Tenofovir and Emtricitabine Five-days-On, Two-days-Off each week in virologically suppressed patients

C. Cohen¹, A. Colson¹, G. Pierone², E. Dejesus³, F. Kinder⁴, R. Elion⁵, D. Skiest⁶, A. Habel⁷, J. Jensen⁷, J. Garb⁷, H. Schrager⁷, D. Back⁸

¹CRI New England, Boston, United States, ²AIDS Research and Treatment Center of the Treasure Coast, Fort Pierce, United States, ³Orlando Immunology Center, Orlando, United States, ⁴Kinder Medical Group, Miami, United States, ⁵Whitman-Walker Clinic, District of Columbia, United States, ⁶CRI New England, Springfield, United States, ⁷Baystate Medical Center, Springfield, United States, ⁸University of Liverpool, Liverpool, United Kingdom

<table>
<thead>
<tr>
<th></th>
<th>FOTO Arm</th>
<th>Daily ART arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number completing follow up</td>
<td>25/30</td>
<td>28/30</td>
</tr>
<tr>
<td>Viral load Blips</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>VL &lt;50c/ml at 24wks</td>
<td>100%</td>
<td>86%</td>
</tr>
</tbody>
</table>

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Cohen C, HIV Clin Trials 2007, 8:1 –23
Cohen C, HIV Clin Trials 2007, 8:256
Cohen C, IAS, 2009; Cape Town., MOPEB063
171 adults VL<50c/ml, EFV based HAART

<table>
<thead>
<tr>
<th></th>
<th>SCT arm</th>
<th>CT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed* at 72weeks</td>
<td>6/52 (11.5%)</td>
<td>11/51 (21.6%)</td>
</tr>
</tbody>
</table>

*Defined as VL>1000 c/ml, decrease in CD4 cell count from baseline of >30% or CD4 count <100, on 2 consecutive occasions through 72 weeks; or at 72 weeks VL>400 or development of an OI
Toxicity Reduced
- Lactic acidosis in d4T recipients
  - 11.4 vs 0/100 pt yrs, p=0.04
- Lipodystrophy
  - 11.4 vs 1.8/100 pt yrs, p=0.13
  - Rate 6.2 times more in CT arm

Resistance - no difference
- 4/5 in SCT & 5/7 in CT
- K103N: 4/4 SCT v 3/5 CT
Young people’s views on SCT

- 40 questionnaires completed (age 8-18yrs) from UK, Italy, Germany, France & Spain

“Would you be interested in taking medicine for 5 days and then having 2 days off?” - 75% said YES

“make my life easier” “sleep in on Sat & Sun”

“a chance to relax” “weekend free”

“because I can go on a sleepover or clubbing without having to take meds”
Breather (PENTA 16) - schematic

8-21 years old, on EFV containing first line regimen with VL<50 for 1 year or more (n = 160)

Randomise (1:1, stratified by age (8-12, 13-17, 18-21))

Continuous
(n=80)

SCT
5 days on; 2 days off
(n=80)

48 weeks
Endpoint
VL > 50 copies/ml
Planned Treatment Interruption

**Hopes**
- ✓ Reduce overall ARV exposure
- ✓ Restore baseline on reintroduction of ARVS
- ✓ Reduce cumulative toxicities
- ✓ Improve adherence and retention in care
- ✓ Enhance quality of Life
- ✓ Reduce cost
- ✓ Increase ARV rollout

**Fears**
- ✗ AIDS events and encephalopathy in infants
- ✗ Rapid decline in CD4 and irreversible immunologic changes
- ✗ Refusal/reluctance to resume therapy
- ✗ Loss of first line therapy
- ✗ Accumulation of resistance mutations
Those who never get into care......

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>ART 2010 WHO ART guidelines</th>
<th>ART 2006 WHO ART guidelines</th>
<th>PMTCT</th>
<th>ART in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>37%</td>
<td>57%</td>
<td>54%</td>
<td>26%</td>
</tr>
<tr>
<td>Latin America &amp; Caribbean</td>
<td>50%</td>
<td>67%</td>
<td>54%</td>
<td>58%</td>
</tr>
<tr>
<td>Asia</td>
<td>19%</td>
<td>31%</td>
<td>93%</td>
<td>49%</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>11%</td>
<td>18%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Global (2009)</td>
<td>36%</td>
<td>52%</td>
<td>53%</td>
<td>28%</td>
</tr>
<tr>
<td>Global (2008)</td>
<td>28%</td>
<td>42%</td>
<td>45%</td>
<td>22%</td>
</tr>
</tbody>
</table>

14.6M in need of treatment (11M in SSA)
9.4M cannot get it

Source: WHO, 2010

Estimated ART coverage in Low and Middle Income Countries by region in 2010
Only 25% children who need ARVs are receiving them

• Of 118 reporting low/middle income countries 38% reported stock outs
  – Africa: 50%
  – Americas: 52%
  – South East Asia 25%
  – Western Pacific 23%
Optimising ARV Strategy for Children

- Diagnosis
- Early Initiation
- Secure ARV Supply
- PTI
Planned Treatment Interruption

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Acknowledgements

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• CHIPS Cohort Study Group
• MRC
• Prof Di Gibb
• Prof Nigel Klein & immunology substudy group
• Colleagues at the Rainbow Clinic, Dublin
• & all the Patients and families of the last 25 years!